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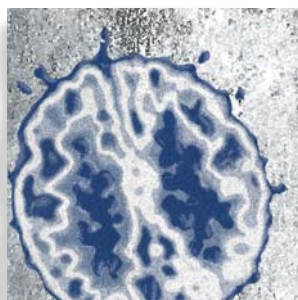
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Pharmacogenomic strategy for individualizing antidepressant therapy

Keh-Ming Lin, MD, MPH; Roy H. Perlis, MD; Yu-Jui Yvonne Wan, PhD



Despite remarkable progress, pharmacotherapy in general, including that for the treatment of depressive conditions, has often ignored the magnitude and clinical significance of the huge interindividual variations in pharmacokinetics and pharmacodynamics, resulting in poor compliance, suboptimal therapeutic effects, and treatment resistance. Advances in pharmacogenomics and computer modeling technologies hold promise for achieving the goals of “individualized” (“personalized”) medicine. However, the challenges for realizing such goals remain substantial. These include the packaging and interpretation of genotyping results, changes in medical practice (innovation diffusion), and infrastructural, financing, ethical, and organizational issues related to the use of new information.

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Despite mounting evidence to the contrary, current pharmacological practices largely ignore or minimize individual and cross-group variations, which often are extremely sizable. Textbooks and package inserts provided by pharmaceutical companies give a fairly narrow range for dosing recommendations. Consequently, medications prescribed in the clinical setting are way too little for some, and grossly excessive for others. There are also currently no rational guidelines for choosing one class or type of medication over the other (eg, selective serotonin uptake inhibitors [SSRIs] vs others). This approach of “one size fits all” is often the reason for poor treatment response, noncompliance, severe adverse effects, unnecessary hospitalization, and even mortality. Pharmacogenetics and pharmacogenomics (PG) hold great potential for addressing these issues. In fact, while the field continues to progress with lightning speed, with much more valuable information still forthcoming, a great deal is already known about factors governing both the pharmacokinetics and pharmacodynamics of many drugs, and the technology is largely there to put these into clinical use.

A number of major obstacles are likely responsible for this apparent discrepancy between the progress of PG on the one hand, and its clinical application on the other. These include (i) feasibility of incorporating PG input into clinical decision-making, which might be termed clinical pharmacogenomics (CPG), and the impact of such an approach on clinical outcome; (ii) complexity and apparent “overabundance” of PG information vis-à-vis drug response; (iii) inherent “inertia” hindering the “diffusion of innovation,” and the need for incorporating PG approaches into medical education; (iv) problems related to the “economy of

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Selected abbreviations and acronyms

AD	<i>antidepressant</i>
CYP	<i>cytochrome P-450 enzyme</i>
PG	<i>pharmacogenetics and pharmacogenomics</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>

scale;" and financial support for new approaches.

In the following article, we will briefly review the literature suggesting that CPG is feasible and clinically relevant, and that depressed subjects treated with the CPG approach will show significantly fewer side effects (greater tolerability), greater treatment adherence, better clinical outcome, and a lower rate of relapse. Such data should be encouraging for medical educators and policymakers in moving forward with the broad adaptation of CPG as part of the standard of care, and the realization of the goals of what have been generally called "individualized" or "personalized" medicine.

The prevalence and impact of clinical depression

Extensive clinical and epidemiological data, accumulated over the past several decades, consistently indicate that clinically significant depression is a highly prevalent condition. Using the Composite International Diagnostic Interview, a revised structured clinical interview instrument derived from the Diagnostic Interview Schedule, the National Comorbidity Study found that up to 25% of the general population in the US are at risk of developing DSM-III-R-defined major depression at least once in their lifetime.¹ Utilizing similarly sophisticated research designs and assessment instruments, a number of well-designed studies also have been conducted in other countries, ranging from France to Korea.² Together, these studies convincingly demonstrate that depression is a worldwide phenomenon, and is a serious public health problem in any society.³

Approximately 15% of the people who suffer from major depression eventually end their lives with suicide,⁴ making suicide one of the ten major causes of death in many countries in recent years. Recent studies have also demonstrated that depression is frequently associated with significant morbidity, mortality, and functional impairment, and often incurs substantial financial costs to society comparable to, or exceeding, many other relatively common medical problems such as hypertension or diabetes.⁵ In addition, recent studies have shown that depression is a major risk factor for other life-threatening medical conditions, such as heart

attacks, stroke, and cancers.^{6,7} Furthermore, although acute depressive episodes are often time-limited, longitudinal follow-up studies conducted in recent years revealed that relapse often occurs, rendering the long-term outcome of such a condition far more ominous. Remission is often incomplete; many continue to suffer from subsyndromal depressive conditions, which also have been shown to be associated with significant functional disability.^{8,9}

Current status of antidepressant treatment: success and limitations

Since the 1950s, a large number of antidepressants (ADs) have been developed, each with proven efficacy in well-designed, placebo-controlled, randomized clinical trials. Starting with the classical tricyclic antidepressants and monoamine oxidase inhibitors, now clinicians also have at their disposal a large array of newer antidepressants, including the SSRIs and the serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as a number of other "novel" antidepressants. These compounds, each with its unique profile, together afford clinicians powerful tools in their attempts to bring patients back from the brink of despair. At the same time, the multiplicity and complexity presented by these diverse agents represent a puzzling challenge for clinicians both young and seasoned. Despite decades of research, it remains unclear why, despite their proven efficacy (with proven superiority compared with placebos), a relatively large proportion of the patients fail to respond to these agents, and why different patients might respond to different agents. In other words, there is at present no reliable method for clinicians to predict, prior to the initiation of treatment, which of the several dozens of ADs might be the best for any particular patient. This plight is further worsened by the fact that there is a significant lag time, up to 4 to 6 weeks, before the full benefit of the medication can be determined. Thus, for each "failed" treatment, substantive and perhaps critical time is lost, which might lead to dire consequence including further deterioration, dropping out, and a further increase of the risk for mortality. Similarly, clinicians currently have little means for determining the optimal starting dose of any of the ADs being prescribed. This is so despite the fact that huge interindividual variations (up to 100 times) have been demonstrated for most, if not all, ADs (and most of the other medications). For a substantive proportion of the patients, the "standard" initial doses (as suggested in package

inserts and in textbooks) represent only a small fraction of the optimal dose needed for therapeutic response, for others, such doses lead to severe side effects. The titration is essentially “trial and error,” time-consuming, and contributes further to the delay in treatment response and recovery. Although the determination of the concentration of drugs and their metabolites in bodily fluids (typically plasma or serum) could be useful in this regard, it is usually not available in clinical settings (it may not be feasible to have “blood level” measurements of various ADs available on a routine basis), and is typically done at steady-state, requiring patients to be on a particular medication for at an extended period of time before the measurement (single dose kinetics is even harder to do and more difficult to interpret in the clinical settings).

Thus, although ADs are efficacious, neither their choice nor the dosing strategy are based on rational principles, leading to substantial “false starts,” delay in response, diminished medication adherence, “under- or overtreatment,” iatrogenic problems, morbidity, and even mortality.

The promise of pharmacogenetics/ pharmacogenomics

In such a context, it may be particularly surprising that knowledge derived from the field of pharmacogenetics/pharmacogenomics has not yet made inroads into enhancing clinicians’ ability to “individualize” or “personalize” pharmacotherapy. Evolving over the past half century, the field of pharmacogenetics has provided the basis for our understanding of many “idiosyncratic” drug reactions. In recent years, it elucidated much of the genetic basis of individual variations in pharmacokinetics (especially genes determining drug metabolism) and pharmacodynamics (therapeutic target responses). Their relevance for ADs is summarized below.

Genes encoding enzymes and other protein products responsible for the fate and disposition of psychotropics (pharmacokinetics)

As is true with many other pharmacological agents, the biotransformation of practically all ADs are primarily mediated by a group of enzymes called cytochrome P-450 enzymes (CYPs) including CYP2D6, CYP2C19, CYP3A, and CYP1A2. Huge individual variations in the activities of these enzymes have long been demonstrated, much of

which have been accounted for with specific allelic variations in the genes encoding these enzymes. For example, CYP2D6 allelic profiles determine whether a particular individual is a poor metabolizer (those with defective genes encoding no enzyme; approximately 2% in Han Chinese and 7% in Caucasians), intermediate metabolizer (those with “less effective” gene; approximately 50% in East Asians), extensive metabolizer (those with “wild-type” alleles; approximately 47% in East Asians) and ultrarapid metabolizer (those with gene duplication or multiplication; about 1% in East Asians and Northern Europeans, but up to 7% in Spaniards and up to 30% in Arabs and Ethiopians).¹⁰ Studies involving desipramine and venlafaxine clearly indicate that these CYP2D6 polymorphisms are mainly responsible for the pharmacokinetics, dosing, and side-effect profiles of these CYP2D6 substrates.^{11,12} Similarly, specific allelic alterations also have been demonstrated to determine CYP2C19 enzyme activities, and consequently the dosing and side effect profiles of medications metabolized by this enzyme. In addition, the activity of some of these CYPs also could be significantly altered by exposure to environmental agents, whose mechanisms also have been elucidated. For example, the induction effect of St John’s wort (and other natural substances) on CYP3A4 is now known to be mediated via the steroid and xenobiotic receptor [SXR], and the induction of CYP1A2 by constituents of cigarettes is mediated through the activation of the Ah receptor.¹³

Although less well documented, a number of genes other than the CYPs also influence the process of pharmacokinetics, and thus are likely to also affect the dosing and side-effect profiles of ADs. These include genes encoding transferases, such as glutathione-S-transferase (GST) and UDP-glucuronosyltransferases (UGTs), which are responsible for drug conjugation; multidrug-resistance gene (MDR1) encoding the P-glycoprotein responsible for exporting lipophilic compounds to the extracellular space (and thus reducing drug absorption in the gut as well as inhibiting their crossing the blood-brain barrier)^{14,15}; and, orosomucoid 1 and 2 (ORM1 and ORM2) encoding the alpha-1-acid glycoproteins responsible for most of the often extensive binding of psychotropics to plasma proteins.^{16,17} (*Table I*)

Genes encoding therapeutic targets of ADs (pharmacodynamics)

A number of monoamine neurotransmitter systems,

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including serotonin (5-HT), norepinephrine (NE), and dopamine (DA), may all play crucial roles in mediating vulnerability to depressive disorders.¹⁸⁻²⁰ Moreover, most of the commonly prescribed antidepressants are believed to exert their effects at least in part through the modulation of either the 5-HT or the NE systems, or both.^{19,20} As the proximal site of action of many antidepressants in clinical use, the genes of the 5-HT, NE, and DA systems therefore represent attractive functional candidates in exploring antidepressant response. Each of these systems is influenced by three types of gene products: (i) those involved in biosynthesis and catabolism of the monoamines; (ii) the receptors mediating their effects; and (iii) the specific transporters which remove them from the synapses.¹⁸ Although a large number of studies have been conducted examining the association between many of these genes and antidepressant response as well as risk for mood and associated disorders, results have often been inconsistent. Of these, however, the serotonin transporter (SERT or 5-HTT) appears most promising. As the target of SSRIs, 5-HTT clearly plays a crucial role in determining patients' response to these antidepressants, and thus it is reasonable to speculate that functional genetic polymorphism(s) should bear clinical relevance. This indeed appears to be the case with the 5-HTT gene-linked polymorphic region (5-HTTLPR), a 44 base-pair insertion/deletion in the promoter region, which significantly influences the basal transcriptional activity of 5-HTT,²¹ resulting in differential 5-HTT expression and 5-HT cellular uptake.²² Hariri et al²³ reported that subjects

who are homozygotic for the *l* allele for 5-HTTLPR showed less fear and anxiety-related behaviors and exhibited less amygdala neuronal activity as assessed by functional magnetic resonance imaging in response to fearful stimuli. In congruence with this, a large number of studies have suggested association between this polymorphism and anxiety, depression and suicide risks. The relationship between 5-HTTLPR polymorphisms and antidepressant response has been intriguing. Seven of nine studies,²⁴⁻³² including one from Taiwan,²⁴ showed that the 5-HTTLPR *l* allele is associated with better or more rapid SSRI response. Two recent studies also implicate the 5-HTTLPR *s* allele in SSRI-emergent adverse effects.^{33,34}

Other genes that have been the target of similar investigations include serotonin_{2A} receptor (*5-HT2A*),³⁵⁻³⁸ dopamine transporter (*DAT1*),³⁹⁻⁴⁶ dopamine D₂, D₃, D₄ receptor (*DRD2*, *DRD3*, *DRD4*), norepinephrine transporter (*NET*), adrenalin_{2A} receptor (*ADRA2A*),⁴⁷⁻⁵⁰ beta adrenalin receptor (*betaARs*),⁵¹ Catechol-*O*-methyltransferase (*COMT*),⁵² monoamine oxidase (*MAO*),⁵³⁻⁵⁵ tryptophan hydroxylase (*TPH*),^{27,56,57} G-protein beta3-subunit (*Gbeta3*),⁵⁸ apolipoprotein E epsilon⁴⁹ and brain-derived neurotrophic factor (*BDNF*).⁶⁰ (Table II)

From pharmacogenomics to individualized medicine

The remarkable advances as described above notwithstanding, the goal of achieving "individualized medicine" remains elusive. Although part of this apparent lack of

Gene	Gene name	Chromosomal location	Size (bp)*	Public Database SNPs	
				# SNPs	Mean distance between SNPs (kb)
Cytochrome P450 1A2	<i>CYP1A2</i>	15q24.1	7776	28	0.6
Cytochrome P450 2C19C	<i>CYP2C19</i>	10q23.33	90209	31	3.2
Cytochrome P450 2D6	<i>CYP2D6</i>	22q13.1	14797	125	0.1
Cytochrome P450 3A4	<i>CYP3A4</i>	7q22.1	27205	66	0.7
Cytochrome P450 3A5	<i>CYP3A5</i>	7q22.1	31790	15	2.7
Constitutive androstane receptor	<i>CAR</i> , <i>NR1I3</i>	1q21.3	8,511	28	0.3
Steroid and xenobiotic receptor	<i>SXR</i> , <i>NR1I2</i>	3q12-q13.3	38,001	69	0.6
Orosomucoid 1	<i>ORM1</i>	9q32	3422	70	0.3
Orosomucoid 2	<i>ORM2</i>	9q32	3230	73	0.3
Multiple drug resistance 1	<i>MDR1</i>	7q21.1	209390	202	1.0
UDP-glycosyltransferase	<i>UGT2B7</i>	4q13.2	16451	0	0
UDP-glycosyltransferase	<i>UGT2B15</i>	4q13.2	23987	46	0.9

Table I. Candidate genes and corresponding single nucleotide polymorphism (SNP) densities (pharmacokinetics).

progress in the clinical application of pharmacogenomics may be attributable to existing gaps in the knowledge base, there is a general belief that the field has progressed to a point that sufficient information has already been accumulated that is clinically applicable. Factors impeding the progress in this direction have to do with infrastructure as well as data showing efficacy and cost-effectiveness of the pharmacogenomic approach.

Development of pharmacogenomic panel(s)

Although for some drug-metabolizing enzymes, such as CYP2D6 and CYP2C19, allelic variations could lead to dramatic functional and health consequences, in the majority of the “candidate genes” for antidepressant response, the influence is partial and may be cumulative. This means that many genes may influence treatment response, but each with only a small effect. This is especially true with genes encoding potential therapeutic targets. Although this has been the consensus in the field for a number of years, the extant pharmacogenetic literature is predominantly based on single genotype or a combination of only a few genotypes. In order for pharmacogenetic data to be clinically useful,

multiple relevant genotypes need to be tested simultaneously, and the results need to be available for clinicians in a timely manner (preferably within 24 hours), such that the data could be included in the clinical decisions made prior to the initiation of pharmacotherapy. With the advent of high-throughput genotyping technologies, this is no longer out of reach. Thus, the next generation of pharmacogenomic research should include the development of specific pharmacogenomic panel(s) for different disease categories and treatment methods.

Developing user-friendly tools for interpreting pharmacogenomic results

Since for any disease/treatment category, such a panel will likely include a large number of “candidate genes,” whose function likely is influenced by multiple alleles, the results of the panel will be exceedingly complex and may not be easily interpretable by typical clinicians, much less readily incorporated into the clinical decision making process. To solve such a problem, a number of modeling programs have been developed. Of these, the most promising appears to be the neural network model

Gene	Gene name	Chromosomal location	Size (bp)*	Public Database SNPs	
				# SNPs*	Mean distance between SNPs (kb)*
5-HT genes					
* Serotonin _{1A} receptor	HTR1A	5q12.3	1269	12	0.8
* Serotonin _{2A} receptor	HTR2A	13q14.2	62661	121	0.6
* Serotonin _{2C} receptor	HTR2C	Xq24	326074	147	2.3
* Serotonin transporter	HTT SLC6A4	17q11.2	24118	33	1.1
* Tryptophan hydroxylase	TPH	11p15.1	19772	53	0.8
NE/DA genes					
* Monoamine oxidase A	MAOA	X-p11.3	70206	51	1.7
* Catechol-O-methyl transferase	COMT	22q11.21	27135	91	0.4
* Adrenergic alpha _{2A} receptor	ADRA2A	10q25.2	3650	22	0.9
* Norepinephrine transporter	NET1 SLC6A2	16q12.2	46031	122	0.5
* Dopamine _{D2} receptor iso l/s	DRD2	11q23.2	65577	98	0.8
* Dopamine _{D3} receptor iso a-d	DRD3	3q13.31	50200	73	0.9
* Dopamine _{D4} receptor	DRD4	11p15.5	3400	20	0.6
* Dopamine _{D5} receptor	DRD5	4p16.1	2032	48	0.4
* Dopamine transporter	DAT SLC6A3	5p15.33	52637	337	0.2
Other novel loci (example)					
* Brain-derived neurotrophic factor	BDNF	11p14.1	42903	30	2.0

Table II. Candidate genes and corresponding single nucleotide polymorphism (SNP) densities (pharmacodynamics/signaling). 5-HT, serotonin; NE, norepinephrine; DA, dopamine

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or neural fuzzy model. Using such a model, relevant genetic data as well as clinical, sociodemographic, and lifestyle variables (past medication response history, concurrent use of other medications, dietary practices, and exposure to other drug-inducing or inhibiting agents, such as cigarette smoking) could be simultaneously incorporated into the estimations for the probability of efficacy and dosing strategy for different medications. Further, a unique feature of such a model is that it is “trainable,” in that as additional relevant data become available, they could be readily incorporated to improve the prediction model.

Pilot intervention project for clinical pharmacogenomics

Once established, such a therapeutic management system (pharmacogenomic panel and the interpreting tool) should then be examined in a series of studies to systematically examine its feasibility, acceptability, effectiveness and ultimately cost-effectiveness. Randomized controlled trials could be designed with consenting subjects randomly assigned to experimental (pharmacogenomically informed) and control (decision based on best current practice guidelines).

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Conclusion

In the past decade, the field of pharmacogenomics has exploded, resulting in a huge body of literature pointing to its promising and imminent clinical application and the realization of the goal of individualizing medical care. That this has not yet taken place is in all likelihood much less related to the incompleteness of information, but to the absence of infrastructure such as the management system discussed above, and consequently the kind of intervention studies examining the clinical utility and cost effectiveness of such an approach. While the more traditional association studies are still needed to further expand our knowledge base, it is also timely that the field starts to explore ways to package knowledge that is already available, and examine their clinical application in well-designed studies. This represents an initial effort in this direction, with the goal of enhancing efficacy, reducing iatrogenic casualties, relieving untoward effects and suffering secondary to delayed treatment response, and ultimately, saving of medical care costs. This may lead to a major breakthrough in understanding with potential for radically changing the way medicine is practiced. □

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Estrategia farmacogenómica para la terapia antidepressiva personalizada

A pesar del notable progreso de la farmacoterapia en general, incluyendo el tratamiento de la depresión, a menudo se ha ignorado la magnitud y el significado clínico de las enormes variaciones inter-individuales en la farmacocinética y farmacodinámica, que favorecen una pobre adherencia, efectos terapéuticos sub-óptimos y resistencia al tratamiento. Han sido significativos los avances recientes en el campo de la farmacogenómica. Las actividades de las principales enzimas del citocromo P-450, incluyendo CYP2D6, CYP2C19, CYP3A4 y CYP1A2 han demostrado que predicen las concentraciones séricas de antidepressivos, la dosificación, los efectos secundarios y tanto las interacciones fármaco-fármaco como fármaco-hierba, y se han identificado los polimorfismos genéticos responsables de la expresión diferencial de estos genes. Asimismo, los polimorfismos genéticos de las proteínas responsables de mediar las respuestas de los antidepressivos, como el polimorfismo de la región promotora del transportador de serotonina (5-HTTLPR), han demostrado que determinan tanto las respuestas terapéuticas como la propensión a los efectos secundarios. Tales avances, apoyados por las tecnologías de modelos computacionales, mantienen las promesas de alcanzar los objetivos de la medicina "individualizada" ("personalizada"). Sin embargo, los desafíos para obtener tales objetivos siguen siendo importantes. Estos incluyen la presentación e interpretación de los resultados de la genotipificación, los cambios en la práctica médica (difusión de la innovación), temas de infraestructura, financieros, éticos y organizacionales relacionados con el empleo de nueva información.

Stratégie pharmacogénomique pour l'individualisation du traitement antidépresseur

Malgré des progrès remarquables, la pharmacothérapie en général, dont celle des états dépressifs, a souvent ignoré l'importance et la signification clinique des importantes variations interindividuelles de la pharmacocinétique et de la pharmacodynamique, conduisant à une observance médiocre, à des effets thérapeutiques sous-optimaux et à une résistance au traitement. Les récents progrès dans le domaine de la pharmacogénomique ont été essentiels. Les activités des principales enzymes du cytochrome P-450, dont les CYP2D6, CYP2C19, CYP3A4 et CYP1A2, ont été montrées susceptibles de prédire les concentrations sériques, le dosage, les effets indésirables et les interactions médicament-médicament comme médicament-plantas (phytothérapie) des antidépresseurs, et des polymorphismes génétiques responsables de l'expression différentielle de ces gènes ont été identifiés. De même, des polymorphismes génétiques des protéines responsables de la médiation de l'effet des antidépresseurs, tel que le polymorphisme de la région promotrice du transporteur de la sérotonine (5-HTTLPR), pourraient déterminer la réponse au traitement ainsi que la propension aux effets indésirables. De telles avancées, soutenues par la modélisation informatique, laissent envisager la possibilité d'atteindre le but d'une médecine « individualisée » (« personnalisée »). Il reste cependant un nombre de défis importants avant d'atteindre ce but : présentation et interprétation des résultats des génotypes, changements dans la pratique médicale (diffusion de l'innovation), problèmes d'infrastructure, de financement, d'éthique et d'organisation liés à l'utilisation d'une nouvelle information.

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